DRAFT

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To: **Dr. Cathy Ellis** **Date: January 22,1998**

From: **Richard Carchman**
Klaus von Holt
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Subject: Preliminary comments on JAMA article 14 Jan. 1998

We have just received a copy of the article entitled ***Cigarette Smoking and Progression of Atherosclerosis*** published in the Journal of the American Medical Association (JAMA; 279, (2): 119-124, authored by Howard et al. This published study represents a partial analysis derived from the Atherosclerosis Risk in Communities (ARIC) population previously described (Amer. J. Epid., 129, (4): pp. 682-702, 1989). ARIC is a multicenter population based investigation of approximately 16,000 individuals (male and female) examined/questioned twice between 1987-1989 in four centers (Minnesota, Maryland, Mississippi, North Carolina). The study population was divided into five groups. Smoking history was obtained by self report. Smokers were then further subdivided as current or past (>100 cigarettes in the past). Never smokers were not characterized further. "Exposure" to environmental tobacco smoke (ETS) for past and never smokers was determined by answering the following question: "During the past year, about how many hours/week, on average, were you in close contact with people when they were smoking? For example, in your home, in a car, at work, or other close quarters." Never and past smokers were classified as exposed to ETS if they reported contact with smokers >1 hour/week. The authors do not report on the use of any objective measures for assessing the validity of recent current or recent past smoking status (e.g., cotinine measurements). Since smoking misclassification is not evaluated, this will impact the validity of authors' inferences. The authors should have evaluated spousal smoking status as it should similarly impact the validity of their analyses (e.g., concordance). The authors' categorization of ETS exposure based on the question used is so limited as to be useless as a metameter for ETS exposure. At best, the question provides some insight into past events (one year) on duration events only. Exposure contains at least one other parameter, i.e., intensity. It is at a minimum the product of intensity and duration derived

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To: **Dr. Cathy Ellis** **Date:** January 15, 1998

From: **Richard Carchman**

Subject: **Preliminary comments on JAMA article 14 Jan. 1998**

I have just received a copy of the article entitled ***Cigarette Smoking and Progression of Atherosclerosis*** published in the Journal of the American Medical Association (JAMA) 279, No. 2, pp. 119-124 authored by Howard et al. This published study represents a partial analysis derived from the Atherosclerosis Risk in Communities (ARIC) population previously described (Amer. J. Epid., 129, No. 4, pp. 682-702, 1989). ARIC is a multicenter population based investigation of approximately 16,000 individuals (male and female) examined/questioned twice between 1987-1989 in four centers (i.e. Minnesota, Maryland, Massachusetts, North Carolina). The study population was divided into five groups. Smoking history was obtained by self report. Smokers were then further subdivided as current or past (>100 cigarettes in the past). Never smokers not characterized further. "Exposure" to environmental tobacco smoke (ETS) for past and never smokers was determined by answering the following question: "During the past year, about how many hours/week, on average, were you in close contact with people when they were smoking? For example, in your home, in a car, at work, or other close quarters." Never and past smokers were classified as exposed to ETS if they reported contact with smokers >1 hour/week. The authors do not report on the use of any objective measures for assessing the validity of recent current or recent past smoking status (e.g., cotinine). Since smoking misclassification is not evaluated, this will impact the authors' inferences. The authors should have evaluated spousal smoking status as it should also impact their analyses. The authors' categorization of ETS exposure based on the question used is so limited as to be useless as a metameter for ETS exposure. At best the question provides some insight into past events (one year) on duration events only. Exposure contains at least one other parameter, i.e., intensity. It is at a minimum the product of intensity and duration derived from objective measurements that are robust enough to even approach the use of the category ETS exposed.

This paper utilizes an ultrasound technique that measures blood vessel wall thickness that according to the authors is a surrogate for atherosclerosis. 'Baseline' measurements were taken in 1987 (Table 1) and then again three years (1989) later and progression of events recorded (Table 1). Judging from the baseline and progression data presented in Table 1 for the different groups evaluated no meaningful group differences are apparent. The blood vessel thickness measured are derived from the common carotid artery only. Other blood vessel measurements were not used because of missing data and greater variability. The evaluation of the ultrasound information were carried out by individuals who were blinded to the patients groupings (e.g., smoker versus non-smoker). The authors state that this process produces a single index of atherosclerosis with improved precision (no data provided). The inclusion of males and females in the measurement of this one blood vessel requires the reader to be aware of different blood vessels effects reported for atherosclerosis as a function of gender. The authors have an ability to

address this question with the data they already have. This type of analysis could be relevant as to the generalizability of this study and or the validity of the authors inferences.

Surprisingly, based on the baseline and progression data provided in Table 1, the authors continued their analysis (see Table 2). The further analyses presented in Table 2 is divided into two sections--section 1 looks at the five groups utilizing three different mathematical models that adjust for other reported risk factors for atherosclerosis. Each model according to the authors have relatively different degrees of sophistication. The authors point out (p.121) "The need for covariant adjustment is supported by the dramatic differences in the prevalence of cardiovascular risk factors and lifestyle variables. Because of these differences in risk factors across smoking categories, the comparison of unadjusted atherosclerosis progression rates across the smoking strata (which shows increased progression rates with increased cigarette smoke exposure) should be made cautiously." It appears from how the authors relate the data derived from their mathematical models that this legitimate concern was abandoned in the comments section of their paper. Furthermore, the nature of the covariants examined in this paper requires some comment. The covariants for cardiovascular disease included:

- hypertension--based on blood pressure measurements or self reported use of antihypertensives;
- LDL cholesterol-measurements;
- Diabetes--blood glucose measurements or self reported use of antidiabetic medications or self report per se;
- Fat intake--by questionnaire; physical activity--by questionnaire;
- Alcohol use--self report; and
- Body mass index--determined objectively.

Individual exclusion/inclusion criteria for this analysis eliminated >5000 subjects from their evaluations. The covariant risk factors used are a mix of quantitative, qualitative, subjective, and objective determinations. Why other covariant risk factors were not incorporated nor the impact of combining such a mixed approach to the risk factors used is not discussed by the authors is unfortunate. It appears that this aspect of their evaluations leaves the serious reader further questioning the real scientific value of their analyses, inferences, and conclusions. The second section of Table 2 groups the comparisons to evaluate the ETS effect, past versus never smokers and current versus past smokers, for each of the three mathematical models used. It is important to note that comparing the outcomes derived from model 3 with models 1 and 2 demonstrates the complexity of these analyses e.g., the ETS effect is $\geq$ than the current and past smoker effect for models 1 and 2, but not for model 3. This suggests the following possibilities:

(1) the very limited value of the covariants used in models 1 and 2, and
(2) that even the more complex model (#3) is still too restrictive in that other important covariants (confounders) remain to be evaluated.

A significant point as to the relevance of Table 2 is the presentation of the data from Table 2 (model #3) in Fig. 1 (p. 122). Unlike the authors' conclusions derived from section 2 (Table 2), Fig. 1 draws the reader to come to a different series of conclusions and further questions the basis

for how the authors aggregated their data for analysis in Table 2 (Section 2). Comparing never smokers with and without ETS "exposure" or past smokers with and without ETS "exposure" no significant differences ("ETS" effect) are found as it might relate to the progression end point. Similarly, there is no statistically significant difference between current smokers and past smokers "exposed" to ETS (Fig. 1). These conclusions are in stark contrast to what the authors conclude and yet this discrepancy is not addressed.

The authors indicate in the text (p. 122) that subjects (never and past smokers) were asked to assess the number of hours of ETS "exposure" and this information was then correlated ("dose-response") with the progression rate. The authors conclude that "there was no evidence of a dose response." Aside from the fact that dose was never determined, the failure to establish a correlation between "dose" and effect (progression) undermines the biological plausibility of the association. The authors try to minimize this discrepancy (p. 123) by undermining the validity of the use of the ETS "exposure" to quantify the number of hours/weeks exposed.

Overall, I found the date, its analyses, and the authors' conclusions weak and contradictory. I believe that all one would be able to say is that there may be certain associations between "exposures" and the endpoint measured. Causality arguments are at best premature; the use of imprecise data collection methods, less than robust analyses, and the inclusion(s) of highly speculative mechanistic scenarios is scientifically unjustified.

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from objective measurements that are robust enough to even approach the use of the category ETS exposed.

This paper reports on the utilization an ultrasound technique that measures blood the median wall thickness (median IMT) of the two inner layers (referred to as the intima and the media) of the carotid artery that, according to the authors, is a surrogate for atherosclerosis. 'Baseline' measurements were taken in 1987 (Table 1) and then again three years (1989) later and progression of events were recorded (Table 1). Judging from the baseline and progression data presented in Table 1 for the different groups evaluated, no meaningful group differences are apparent. The blood vessel thickness measured are derived from the common carotid artery only. Other blood vessel measurements were not used because of missing data and greater variability. The evaluation of the ultrasound information was carried out by individuals who were blinded to the patients groupings (e.g, smoker versus non-smoker). The authors state that this process produces a single index of atherosclerosis with improved precision based on epidemiological results (referencing a recent publication from the ARIC group to be further discussed below, Amer. J. Epid. 146, (6): 483-494, 1997).

Mechanistically there are numerous problems with both the assumptions and the claims made relating the median IMT to the development of atherosclerosis. First of all, carotid IMT data, such as those reported by Howard, et al., are not measurements of atheroscherosis. Atherosclerosis is primarily a disease of the intima, the thin innermost layer of the arteries, not of the media. There are pathological processes other than atherosclerosis which can thicken the media. Measurements of intima-media thickness do not distinguish between arterial thickening due to atherosclerosis (which is mainly related to intimal changes) and nonatherosclerotic thickening (which is mainly related to medial changes). The degree to which IMT data, which reflect overall thickening of the intima-media layers, might measure atherosclerosis is seriously debated in the literature (Wendelhag, I., Wiklund, O., and Wikstrand, J., "Arterial Wall Thickness in Familial Hypercholesterolemia, Ultrasound Measurement of Intima-Media Thickness in the Common Carotid Artery," Arteriosclerosis and Thrombosis, 12: 70-77, 1992; Bots, M. L., Hofman, A., DeJong, P. T. V. M., and Grobbee, D. E., "Common Carotid Intima-Media Thickness as an Indicator of Atherosclerosis at Other Sites of the Carotid Artery. The Rotterdam Study," Ann. Epidemiol., 6: 147-153, 1996; Grobbee, D. E., and Bots, M. I., "Carotid Artery Intima-Media Thickness as an Indicator of Generalized Atherosclerosis," Journal of Internal Medicine, 236(5): 567-573, 1994; Bonithon-Kopp, C., Touboul, P.-J., Berr, C., Leroux, C., Mainard, F., Courbon, D., and Ducimetiere, P., "Relation of Intima-Media Thickness to Atherosclerotic Plaques in Carotid Arteries. The Vascular Aging (EVA) Study," Arterioscler. Thromb. Vasc. Biol., 16: 310-316, 1996).

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Secondly, it should be noted that the carotid IMT data reported by Howard, et al., including the IMT data on active smokers, were all far below thicknesses considered in the literature, including in previous ARIC research, to reflect atherosclerotic plaque. One way to attempt to distinguish atherosclerotic plaque from a general thickening of the carotid artery wall is to use a cut-off point, above which the thickening would be classified as atherosclerosis. The literature has proposed several possible values. It has been suggested, for example, that "[v]alues exceeding 3 or 4 mm [3000-4000 microns] probably reflect eccentric thickening or atherosclerotic plaque." (Bonithon-Kopp, C., Touboul, P.-J., Berr, C., Leroux, C., Mainard, F., Courbon, D., and Ducimetiere, P., "Relation of Intima-Media Thickness to Atherosclerotic Plaques in Carotid Arteries. The Vascular Aging (EVA) Study," Arterioscler. Thromb. Vasc. Biol., 16: 310-316, 1996, p. 314 col. 2.) In a 1991 ARIC case-control study examining risk factors for carotid atherosclerosis, carotid IMT of 1.6 mm [16700 microns] was used to define atherosclerosis "cases." (Heiss, G., Sharrett, A. R., Barnes, R., Chambless, L. E., Szklo, M., Alzola, C., and the ARIC Investigators, "Carotid Atherosclerosis Measured by B-Mode Ultrasound in Populations: Associations with Cardiovascular Risk Factors in the ARIC Study," American Journal of Epidemiology, 134(3): 250-256, 1991.) Other investigators have suggested an even lower cut-off. For example, a well-known Dutch study involving ultrasound data on carotid IMT proprosed 0.90 mm [900 microns] as a point below which IMT measurements would reflect "non-plaque-related wall thickening due to a more generalized process, possibly including medial hypertrophy." (Grobbe, D. E., and Bots, M. L., 1994.) By comparison, all of the baseline IMT measurements reported by Howard, et al., were in a range of 626 to 657 microns. Moreover, even if IMT increased during the three-year follow-up as claimed by Howard, et al, these levels would have still been under 700 microns, and therefore well below the values suggested in the literature, including in previous ARIC research, to reflect atherosclerotic plaque.

The IMT values reported by Howard, et al., are further put into perspective when considering that these values were low, even for normal nonatherosclerotic carotid arteries. A 1993 review assessing carotid ultrasound techniques as potential tools in atherosclerosis research noted:

> The average thickness of the combined media and intima in a normal CCA [common carotid artery] varies in middle-aged men between 0.7 and 1.2 mm [700-1200 microns], depending on age. (Salonen, J. T., and Salonen, R., "Ultrasound B-Mode Imaging in Observational Studies of Atherosclerotic Progression," Circulation, 87(Suppl. II): II-56-II-65, 1993.)

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Although the 700-1200 micron range is given for men, and the Howard, et al., report included both men and women, it is apparent that the IMT levels they reported (averaging 644 microns at baseline) would be considered low, even for "normal" carotid arteries.

Lastly it should be noted that carotid IMT measurements in the ARIC study were made in areas of the carotid arteries where atherosclerosis usually does not develop. This calls into question the relevance of these data, not only for claims about coronary atherosclerosis, but for carotid atherosclerosis as well. There are two carotid arteries, which rise to the brain on each side of the neck. The initial segments of these arteries are the right and left common carotid arteries. Each splits into branches referred to as the internal and external carotids. Atherosclerosis in the carotid arteries most often occurs in the vicinity of the branching or in the internal carotid arteries. Despite this, the Howard, et al., report is based on common carotid artery measurements. Other carotid IMT studies have also frequently restricted measurements to the common carotids, even though atherosclerosis rarely occurs there, and whatever intima-media thickening develops may not be pathogenically similar to actual atherosclerotic plaque seen elsewhere in the carotid circulation. The fundamental reason for projects such as the ARIC study to focus on IMT based on the common carotid arteries is relative ease and reproducibility of measurement. However, these advantages are potentially at the expense of pathological and clinical relevance.

> Despite the lesser atherosclerotic involvement in the CCA, it has increasingly become the 'site of choice' for measurement of initima-media thickness because it is far easier to image reliably than other segments. (Bonithon-Kopp, C., et al., 1996.)

Despite the myriad of reasons, some of which have been discussed above, which suggest that the authors' data are not a meaningful predictor for atherosclerosis, the authors claim that the epidemiological results regarding progression of median IMT not only support such a relationship ~~(Chambless, et al., Amer. J. Epidemiol., 1997)~~ but also demonstrate that both active smoking and ETS exposure are risk factors for atherosclerosis. The authors present their results on the association of progression of median IMT with ETS exposure in Table 2. The analyses presented in Table 2 are divided into two sections--section 1 looks at the five groups utilizing three different mathematical models that adjust for other reported risk factors for atherosclerosis. Each model according to the authors has relatively different degrees of sophistication. The authors point out (p.

121) "The need for covariant adjustment is supported by the dramatic differences in the prevalence of cardiovascular risk factors and lifestyle variables. Because of these differences in risk factors across smoking categories, the comparison of unadjusted atherosclerosis progression rates across the smoking strata (which shows increased progression rates with increased cigarette smoke exposure) should be made cautiously." It appears from how the authors relate the data derived from their mathematical models that this legitimate concern was abandoned in the comments section of their paper. Furthermore, the nature of the covariants examined in this paper requires some comment. The covariants for cardiovascular disease included:

- Hypertension--based on blood pressure measurements or self-reported use of antihypertensives;
- LDL cholesterol was estimated from blood chemistry determinations;
- Diabetes--blood glucose measurements or self-reported use of antidiabetic medications or self report per se;
- Fat intake--by questionnaire;
- Physical activity--by questionnaire;
- Alcohol use--self report, and
- Body mass index--determined objectively.

Individual exclusion/inclusion criteria for this analysis eliminated >5000 subjects from their evaluations. The covariant risk factors used are a mix of quantitative, qualitative, subjective, and objective determinations. Why other covariant risk factors were not incorporated nor the impact of combining such a mixed approach to the risk factors used is not discussed by the authors and is unfortunate. Carotid IMT has been associated with numerous potential confounding factors not discussed by the authors. HDL and other lipoprotein ratios or sub-fractions were not controlled for. Dietary antioxidants, a potential risk factor for increased carotid IMT based on previously reported ARIC data (Kritechevsky, S. B., Shimakawa, T., Tell, G. S., Dennis, B., Carpenter, M., Eckfeldt, J. H., Peacher-Ryan, H., and Heiss, G., "Dietary Antioxidants and Carotid Artery Wall Thickness. The ARIC Study," Circulation, 92: 2142-2150, 1995), were not taken into account. Also, although Howard, et al., attempted to adjust their data for educational level, they did not adjust for income level, nor for occupational class. They also did not adjust for overall socioeconomic status, which has been reported to be a potential risk factor for increased IMT in prior ARIC data (Diez-Roux, A. V., Nieto, F. J., Tyroler, H. A., Crum, L. D., and Szklo, M., "Social Inequlaities and Atherosclerosis. The Atherosclerosis Risk in Communities Study," Am. J. Epidemiol., 141(10): 960-972, 1995) and other

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carotid IMT research (12) (Lynch, J., Kaplan, G. A., Salonen, R., Coehn, R. D., and Salonen, J. T., "Socioeconomic Status and Carotid Atherosclerosis," Circulation, 92: 1786-1792, 1995). Additional uncontrolled psychosocial factors, such as social support and marital status (13) (Helminen, A. Rankinen, T., Mercuri, MN., and Rauramaa, R., "Carotid Atherosclerosis in Middle-Aged Men. Relation to Conjugal Circumstances and Social Support," Scand. J. Soc. Med., 23(3): 167-172, 1995) and psychological stress (14) (Spence, J. D., Barnett, P. A., Manuck. S. B., and Jennings, J. R., "Psychological Stress and the Progression of Carotid Atherosclerosis," Stroke, 27(1): 194, 1966) have been reported to be risk factors for increased carotid IMT, as has occupational stress in previously-reported ARIC data (15) (Muntaner, C., "Occupational Stress and Atherosclerosis: Findings from the ARIC Study," Presented at: Work, Stress and Health '95: Creating Healthier Workplaces, Washington, D. C., September 14-16, 1995). It appears that this aspect of their evaluations leaves the serious reader further questioning the real scientific value of their analyses, inferences, and conclusions.

The second section of Table 2 groups the comparisons to evaluate the ETS effect, past versus never smokers and current versus past smokers, for each of the three mathematical models used. It is important to note that comparing the outcomes derived from model 3 with models 1 and 2 demonstrates the complexity of these analyses e.g., the ETS effect is $\geq$ than the current and past smoker effect for models 1 and 2, but not for model 3. This suggests the following possibilities:

(1) the very limited value of the covariants used in models 1 and 2, and
(2) that even the more complex model (#3) is still too restrictive in that other important covariants (confounders) remain to be evaluated.

The 11 % increase seen in IMT over three years attributed to ETS "exposure" corresponds to the amount of thickening of the artery wall which happens naturally in the aging process over a period of three-four months (see p. 124 - authors comments). The toxicological (pathological) relevance of this change appears to be minor. Thickening of the arterial walls, even the confirmed presence of atherosclerotic plaque, does not necessarily mean that the channel through which the blood flows, the arterial lumen, is significantly narrowed. Luminal diameter is important because symptomatic cardiovascular disease is often considered to be mainly related to luminal narrowing. The relationships between cardiovascular risk factors, arterial wall thickening, and luminal narrowing are complex. Even ARIC data, reported in 1996, indicated that although cigarette smoking was associated with increased common carotid IMT, smoking was actually associated with arterial enlargement in terms of luminal diameter. The ARIC investigators emphasized that the association of risk factors, including smoking, with luminal diameters is "more complex" than the risk factor relationships with IMT, and that "in some

cases adverse levels of risk factors may be associated with larger lumens." (Crouse, J. R., Goldbourt, U. Evans, G., Pinsky, J., Sharrett, A. R., Sorlie, P. Riley, W., and Heiss, G., "Risk Factors and Segment-Specific Carotid Arterial Enlargement in the Atherosclerosis Risk in Communities (ARIC) Cohort," Stroke, 27: 69-75, 1996.)

The quality of the ETS-related data reported by Howard, et al., is extremely low, because of inadequate ETS exposure estimates, lack of evidence for a dose-response relationship and a claimed magnitude of effect below the detection limits of the study, in view of its methodological weaknesses related to measurement error and potential confounding.

The ETS exposure data in the Howard, et al., report were based on a very crude self-report estimate. The ARIC study participants were asked to estimate how many hours per week they had been exposed to ETS in the last year. This method of estimating ETS exposure raises serious scientific questions about the accuracy of recall generally and about whether biases related to selective recall might have been introduced into the study. Beyond the broad issue of weaknesses in self-report data, the ARIC study participants were only asked about ETS exposure during the previous year. This would not take into account variations in exposure during a person's lifetime prior to that, much less variations in ETS exposure that may have occurred during the ARIC follow-up.

The Howard, et al., report acknowledged that there was no relationship of the amount of ETS exposure with IMT progression. The authors stated:

> In an analysis conducted using the lifestyle model, there was no evidence of a dose-response relationship between increasing weekly hours of ETS exposure and increased progression rates (p=0.38) among those exposed to ETS.

Although Howard, et al., downplayed the lack of a dose-response because of possible "differential measurement error" concerning the amount of ETS exposure, it is important to note that previous ARIC research attempting to identify a dose-response relationship of ETS exposure with IMT also failed to do so (Diez-Roux, A. V., Nieto, F. J., Com,stock, G. W., Howard, G., and Szklo, M., "The Relationship of Active and Passive Smoking to Carotid Atherosclerosis 12-14 Years Later," Preventative Medicine, 24: 48-55, 1995).

Finally, there is the issue of whether the extraordinarily tiny magnitudes of effect claimed are scientifically meaningful. The active smoking and ETS exposure IMT differences reported by Howard,

et al., were at the micron level, that is, in terms of millionths of a meter. This raises a serious methodological issue of whether such claimed effects are within the limits of ultrasound resolution and, if so, whether they carry any clinical significance. The ability of ultrasound techniques to provide reliable measurements in the micron range is scientifically questionable. It has been observed, for example, that:

> [M]ost studies measure IMT in individuals to the nearest 0.1 mm [100 microns] or even 0.01 mm [10 microns], which may be beyond the limits of resolution of the ultrasound used. As the intima-media distances being measured are small, most groups have reported interobserver and interoperator variations of 5% to 10%, usually corresponding to actual IMT measurement variations of 0.03 to 0.07 mm [30 to 70 microns].[18] (Adams, M. R., Nakagomi, A., Keech, A., Robinson, J., McCredie, R., Bailey, B. P., Freedman, S. B., and Celermajer, D. S., "Carotid Intima-Media Thickness Is Only Weakly Correlated with the Extgent and Severity of Coronary Artery Disease," Circulation, 92: 2127-2134, 1995.)

The minute differences reported by Howard, et al., need to be evaluated in light of the above resolution limits and measurement variability. For example, the widest three-year group difference in IMT progression rates was only 17.1 microns. (Current smokers, at 43 microns, vs. never smokers not exposed to ETS, at 25.9 microns.) The three-year effect claimed for ETS (an IMT difference of 5.9 microns) was incredibly small. Both the reported active smoking and ETS effects appear to be well below the resolution limits and variability in ultrasound measurements. Whether these tiny differences are scientifically reliable is highly debatable.

In light of the above methodological criticisms, it is worthwhile to look more closely at the authors' claims that progression of median IMT is an excellent predictor of future CVD incidence (Chambless, et al., 1997). In the present study the authors state that a comparison of the rate of CVD incidence in women increases from 0.6 in individuals with a median IMT of <0.6mm to 11.7 in women with a median IMT of > or equal to 1.0mm. If one looks at the data presented in the Chambless paper, however, a different picture emerges. The incidences of CHD as a function of median IMT are: 0.6 for IMT <0.6mm; 1.8 for IMT between 0.6 and 0.7mm; 3.4 for IMT between 0.7 and 0.8mm; 3.8 for IMT between 0.8 and 1.0mm; and 11.7 for IMT greater or equal to 1.0mm. These data cannot be said to indicate a relationship between risk of CHD and median IMT below 1.0mm, because the incidence does not increase monotonically, and because the three central values are not statistically different from one another. In addition, even the incidence of CHD at median IMT values greater than 1.0mm

is not necessarily meaningful, since one cannot examine the upper part of the range. Lastly, it should be noted that the region where a real increase in CHD incidence is noted, that is greater or equal to 1.0mm, is much greater than is seen for the groups reported in the present Howard, et al., study.

Overall we found the data, their analyses, and the authors' conclusions weak and contradictory. We believe that all one would be able to say is that there may be certain associations between "exposures" and the end points measured. Causality arguments are at best premature. The use of imprecise data collection methods, less than robust analyses, and the inclusion(s) of highly speculative mechanistic scenarios are scientifically unjustified.

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Points

- ETS exposure not measured:
  based on questionnaire regarding how long an individual was around smokers
- No relationship between authors ETS "exposure" estimate and blood vessel thickening - i.e. diminishes the biological plausibility of this association
- Natural (age related) thickening of blood vessel wall is significant (surprised authors) and makes the significance of the reported effects questionable
- Baseline blood vessel thickness does not appear to show an association with smoking (Table 1)
- Depending on the mathematical models used different inferences can be made - i.e. no consistent conclusion
- A more consistent association between blood vessel thickening and smoke (active and ETS) "exposure" is only apparent after multiple corrections for various confounding factors. However, the details of this procedure and the sensitivity of its outcome on the assumed prevalence of these factors is not shown.
- Complex incomplete and imprecise measures of risk factors used
- Lack of sufficient detail to evaluate the robustness of the ultrasound data used for their estimation of blood vessel thickness and progression. Recent publication on model validity by ARIC members under WSA review.
- Generalizability of reported effects in male and females is uncertain based on reported (by authors) gender related differences in effected blood vessels.

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13. Helminen

(14) Spence

15. Muntaner

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